第15回国際協力遺伝病遺伝子治療フォーラム

The 15th International Collaborative Forum of Human Gene Therapy for Genetic Disease

The New Future of Gene & Cell Therapy

-Toward the Cure of Hereditary Diseases-

遺伝子細胞治療の新しい未来

～遺伝性疾患の根治を目指して～

Date
開催日

Friday, January 24th, 2025
2025年1月24日(金)

Venue
会　場

The Jikei University School of Medicine, Building 1 Hall
東京慈恵会医科大学　1号館講堂

President
当番幹事

Hiroshi Kobayashi M.D. (The Jikei University School of Medicine)
小林 博司（東京慈恵会医科大学 総合医科学研究センター遺伝子治療研究部 教授）

Program & Abstracts

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Program

9:00 ～ 9:10 **Opening Remarks**

小林　博司 (第 15 回当番幹事　東京慈恵会医科大学 遺伝子治療研究部)
小野寺雅史 (代表幹事　国立成育医療研究センター)

9:10 ～ 9:40 **session 1**

Gene Therapy for Neurological disorder（神経疾患に対する遺伝子治療）

座長：山形　崇倫

9:40 ～ 10:40 **session 2**

Gene Editing and mRNA Therapeutics（遺伝子編集と mRNA 医薬）

座長：村松　一洋　　村松　慎一

10:40 ～ 11:40 **session 3**

Gene Therapy for Inherited Retinal Dystrophy（遺伝性網膜疾患に対する遺伝子治療）

座長：池田　康博　　西口　康二

11:50 ～ 12:40 **session 4（共催セミナー 1）**

Luncheon Seminar【Takara Bio Inc.】: AAV mediated Gene Therapy for Congenital Deafness（遺伝性難聴に対する AAV ベクターを用いた遺伝子治療）

座長：小野寺雅史

12:50 ～ 13:50 **session 5**

Ex vivo Gene Therapy for Inborn Error of Metabolism (先天代謝異常症に対する *ex vivo* 遺伝子治療)

座長：樋口　　孝　　奥山　虎之

13:50 ～ 14:50 **session 6**

In vivo Gene Therapy for Inborn Error of Metabolism (先天代謝異常症に対する *in vivo* 遺伝子治療)

座長：大橋　十也　　鐘ヶ江裕美

15:00 ～ 15:50 **session 7 (共催セミナー2)**

Sweets Seminar【Vector Builder Japan Inc.】: Trial of Gene Therapy for Inborn Error of Copper Metabolism (銅代謝異常に対する遺伝子治療の試み)

座長：小須賀基通

15:50 ～ 16:50 **session 8**

Gene Therapy for neuromuscular disorder（神経筋疾患に対する遺伝子治療）

座長：小坂　仁　岡田　尚巳

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Alex Murphy（ロシュ社臨床開発担当者）WEB

2) Clinical development of Onasemnogene abeparvovec and Voretigen neparvovec（オナセムノゲン アベパルボベク、ボレチゲン ネパルボベクの臨床開発）.....32

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（ノバルティスファーマ株式会社　神経科学・遺伝子治療臨床開発

Novartis Pharma K.K　Neuroscience & GTx Clinical Development）

16:50 ～ 17:40 **session 9（共催セミナー 3）**

Afternoon Seminar【Sanofi】：Genetic Counseling（遺伝カウンセリング）遺伝子治療の道しるべ　ー患者と家族に寄り添うためにー

座長：小林　博司

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稲垣　夏子 (Natsuko Inagaki)

（東京医科大学　循環器内科学分野 Tokyo Medical University, Department of Cardiology

東京医科大学病院　遺伝子診療センター Tokyo Medical University Hospital, Clinical Genetics Center）

17:40-18:30 **session 10**　特別講演

座長：衛藤　義勝

Special Lecture by Professor Luigi Naldini（ヨーロッパ遺伝子細胞治療学会理事長 Naldini 教授による特別講演）.....36

Prof. Luigi Naldini

18:30-18:40 **Closing Remarks**

森下　竜一（日本遺伝子細胞治療学会理事長）

小坂　仁（次回第 16 回当番幹事　自治医大小児科学講座教授）

Gene therapy for neurological diseases

-Abstracts & Curriculum Vitae-

Gene therapy for AADC deficiency

Wuh-Liang Hwu

Distinguished Research Fellow, Center for Precision Medicine, China Medical University Hospital, and Professor Emeritus, Department of Pediatrics, National Taiwan University, Taiwan

Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare genetic neurological disorder arising from biallelic pathological variants in the dopa decarboxylase gene. Deficiency of the AADC enzyme leads to an inability to synthesize dopamine and serotonin, and patients suffer from movement disorders, oculogyric crisis, and autonomic dysfunction. From 26 subjects who received the treatment and have completed 1-year evaluations, rapid improvements in motor and cognitive function occurred within 12 months after gene therapy and were sustained during follow-up for >5 years. An increase in dopamine production was demonstrated by PET and neurotransmitter analysis. Patient symptoms (mood, sweating, temperature, and oculogyric crises), patient growth, and patient caretaker quality of life improved. Although improvements were observed in all treated participants, younger age was associated with greater improvement. There were no treatment-associated brain injuries, and most adverse events were related to underlying disease. Post-surgery complications such as cerebrospinal fluid leakage were managed with standard of care. Most patients experienced mild to moderate dyskinesia that was resolved in a few months. Similar results were found in a study of a more genetically diverse population (n = 6) in Japan. Recently, an open-label trial was conducted in the US to address the safety of the SmartFlow ventricular cannula for administering of the drug to pediatric subjects. Therefore, the world experiences of intraputaminal infusion of AAV2-hAADC for patients with AADC deficiency are rapidly accumulating. Early treatment is important, which will rely on the recognition and diagnosis of the disease by physicians, especially pediatric neurologists.

In vivo genome editing treatment for monogenetic diseases

Tsukasa Ohmori

Professor, Department of Biochemistry, Jichi Medical University School of Medicine
Director, Center for Gene Therapy Research, Jichi Medical University

Gene therapy and genome editing are gaining attention as next-generation treatment strategies for intractable diseases. Adeno-associated virus (AAV) vectors are the most used modality for *in vivo* gene transfer to the liver. Indeed, several AAV vector-mediated gene therapies for hemophilia have been approved by the EMA and FDA. However, the clinical response to AAV vector gene therapy for hemophilia A has decreased over time. It has been suggested that this decline may be due to cytotoxic effects, such as endoplasmic reticulum stress, caused by the expression of coagulation factor VIII (FVIII) in hepatocytes. Moreover, hemophilia A gene therapy requires high dose of AAV vectors than hemophilia B gene therapy. To address these challenges, we have focused on modifying FVIII protein. Our modified FVIII exhibited high activity and secretion, resulting in an increase in coagulation factor activity to therapeutic levels at just 1/30th of the dose used for Roctavian® in macaque experiments. A limitation of AAV vector-based gene therapy targeting the liver is its neonatal application: AAV vectors do not integrate into chromosomal DNA and are therefore not effective during childhood, when hepatocytes are actively proliferating. This makes genome editing a more appropriate option for early childhood liver diseases. We have successfully improved survival of protein C deficient mice with neonatal genome editing therapy, but not conventional AAV-mediated gene therapy. In this symposium, I will introduce our approach to *in vivo* gene therapy and genome editing targeting the liver and discuss the prospects for these technologies in the treatment of genetic diseases.

mRNA Platform Introduction

Patrick Finn, PhD

Vice President, Rare Research & Preclinical Development Moderna

Messenger RNA (mRNA) technology offers a groundbreaking approach to creating new medicines by leveraging the body's own cellular machinery to produce therapeutic proteins. This novel modality, built on a fully integrated mRNA platform, encompasses three critical components: mRNA design, delivery systems, and scalable manufacturing processes. Together, these steps enable efficient development and production of diverse therapeutic candidates.

The platform begins with the rational design of mRNA sequences, utilizing advanced chemistry, sequence engineering, and targeting elements to achieve the intended protein expression. Effective delivery is equally crucial, with lipid nanoparticles (LNPs) serving as optimized carriers to ensure mRNA stability, cellular uptake, and functional protein translation. Finally, robust, reproducible manufacturing processes for mRNA and LNPs enable scalability, a key feature for clinical development across therapeutic applications.

Once successfully established, this mRNA platform can be applied repeatedly across numerous modalities. Applications include prophylactic vaccines, cancer vaccines, localized intratumoral immuno-oncology, regenerative therapeutics, systemic secreted and cell surface therapies, and intracellular therapeutics. The platform's ability to accelerate research timelines, improve technical success rates, and enhance manufacturing efficiency positions it as a transformative tool to address unmet medical needs in a scalable and sustainable manner.

Development of mRNA therapeutics for propionic acidemia and methylmalonic acidemia

Kaku Saito

Senior Director, Clinical Development, Moderna Japan

Rare inherited metabolic disorders such as Methylmalonic Acidemia (MMA) and Propionic Acidemia (PA) present lifelong challenges due to multisystem organ involvement, including the brain, heart, and kidneys. Manifesting as early metabolic crises and progressing to long-term complications like neurological damage and organ failure, these conditions have limited treatment options, underscoring a high unmet medical need.

Moderna is advancing mRNA therapeutics to address these challenges. Investigational mRNA-3705 and mRNA-3927 utilize lipid nanoparticle (LNP) encapsulation to deliver mRNA encoding key metabolic enzymes. mRNA-3705 encodes methylmalonyl-CoA mutase (MUT), and mRNA-3927 encodes PCCA and PCCB subunits of propionyl-CoA carboxylase, aiming to restore deficient enzymatic functions.

The Phase 1/2 mRNA-3705-P101 study demonstrated dose-dependent reductions in methylmalonic acid levels, a key biomarker, with no observed dose-limiting toxicities. Adverse events were primarily mild or moderate (CTCAE grades 1–2), with only one serious adverse event (SAE) reported as drug-related. Initial clinical data suggest potential reductions in the frequency of metabolic decompensation events (MDEs) at therapeutic doses.

Similarly, mRNA-3927-P101, a dose-optimization study for PA, demonstrated no dose-limiting toxicities. Treatment-emergent adverse events (TEAEs) were reported in 15/16 participants, with manageable infusion-related reactions occurring in less than 6% of doses. Early data indicate decreased MDE frequency post-treatment compared to pre-treatment periods.

These studies highlight the safety, tolerability, and early efficacy of mRNA-based therapies, paving the way for transformative treatments in rare metabolic disorders. Ongoing enrollment and dose optimization/dose expansion aim to further refine their therapeutic potential

Startup-driven development of gene therapy for vision restoration using optogenetics

Yusaku Katada MD, PhD

CEO, Restore Vision Inc.
Project Assistant Professor, Department of Ophtalmology, Keio University School of Medicine

Retinitis pigmentosa (RP), one of the leading causes of blindness among young people in Japan, is characterized by the progressive degeneration of photoreceptors and retinal pigment epithelial cells, while the neural pathways to the brain remain intact. Optogenetics, an innovative technology that introduces photosensitivity into surviving retinal cells, has emerged as a promising therapeutic approach. Since the proof-of-concept study was demonstrated in rodent models in 2006, advancements in photosensitive protein engineering and viral vector delivery systems have brought this therapy significantly closer to clinical application.

Internationally, major achievements include France's GenSight Biologics, which reported partial visual recovery in an RP patient. In Japan, although Tohoku University and Astellas Pharma previously explored development, no products have yet received regulatory approval. However, through collaborative research between Keio University and Nagoya Institute of Technology, a novel optogenetic gene therapy leveraging chimeric rhodopsin has been developed to overcome conventional challenges, and clinical trials are now on the horizon.

Due to the complexity of gene therapy, the frontlines of development are increasingly led by startups, which utilize their innovative agility to drive progress, rather than large pharmaceutical companies. University-based startups play a critical role in translating research findings into clinical applications, bridging the gap between basic science and practical treatment.

In this presentation, the speaker will share first-hand experiences and specific case studies to highlight the cutting edge of optogenetic gene therapy development.

Social implementation of gene therapy for inherited retinal dystrophy in Japan

Kaoru Fujinami

Affiliation: Laboratory of Visual Physiology, National Institute of Sensory Organs, National Hospital Organization, Tokyo Medical Centre
Address: 2-5-1, Higashigaoka, Meguro-ku, Tokyo, 152-8902, Japan
Title: Director/professor

Inherited retinal dystrophy (IRD) is a broad group of inherited disorders mainly affecting the retina. IRD is a Mendelian disorder with a strict definition, including various phenotypes such as retinitis pigmentosa, macular dystrophy, and others. IRD is an intractable disease and a major cause of blindness in children and adults. Ocular symptoms include night blindness, visual field constriction, visual acuity reduction, photophobia, colour vision abnormality, etc. Due to the phenotypic and genotype heterogeneity, establishing genotype-phenotype correlations has still been challenging, and there has been no effective treatment for IRD.

Various therapeutic approaches have been developed, along with recent advancements in genome sequencing and molecular biological technologies, gene therapy (supplementation, editing, adding), RNA therapies, pharmacological agents, regenerative cell therapies, and retinal prostheses. Especially, personalized medicine based on genetic diagnosis has been drastically developed, and the first gene therapy drug, voretigene neparvovec-rzyl (VN), was approved in the US in 2017, followed by the EU in 2018 and other countries. In Japan, a phase 3 clinical trial of VN for RPE65-retinopathy was initiated in 2019, and the VN was approved/reimbursed in May/August 2023. At the same time, insurance-covered genetic testing, the PrismGuide IRD Panel system, was also approved. Accordingly, guidelines for the practical use of VN, genetic testing, and others were issued by the working group of the Japanese Vitreous Retinal Society.

The social implementation of genetic diagnosis and gene therapy of IRD in Japan will be illustrated to welcome a new treatment era.

Development of AAV Gene Therapy Targeting GJB2 Related Hearing Loss by Capsid and Promoter Modification

Kazusaku KAMIYA

Associate Professor, Department of Otorhinolaryngology, Juntendo University Faculty of Medicine

Mutation of GJB2 is the most frequent cause of hereditary deafness worldwide and accounts for up to 50% of non-syndromic sensorineural hearing loss. GJB2 encodes connexin 26, a component of cochlear gap junctions that help maintain ion balance in the cochlea. We previously demonstrated that GJB2 deficiency in mice impairs auditory function (Kamiya, J. Clin. Invest., 2014) and that immediate postnatal delivery of wild-type GJB2 to the inner ear via adeno-associated virus (AAV) vector restored the hearing loss in mice by the injection at early postnatal period (Iizuka, Hum. Mol. Genet., 2015). The early postnatal period in mice corresponds to the embryonic period of inner-ear development in humans. Thus, to develop a feasible clinical approach for human gene therapy, mature mice should be used for delivery of AAV to the inner ear. We generated several AAV capsids that effectively infect cochlear supporting cells by shuffling capsid sequences between wild serotypes or directed evolution with the AAV library. And the promoters were modified to express only in GJB2 expressing cells and form proper gap junctions. Then the vectors were tested with adult GJB2 deficient mice and our supporting cell model derived from human patient iPS cells with typical GJB2 mutation (Fukunaga, Stem Cell Reports, 2016, Hum. Mol. Genet. 2021). The modified AAV-mediated delivery of GJB2 significantly restored hearing loss in mature GJB2-deficient mice. Gap junction recovery was confirmed in both animal (GJB2 deficient mice) and cellular models (Patient iPS derived model cells).These results suggest that this capsid/promoter modified AAV–mediated delivery of functional GJB2 could potentially restore hearing to patients with GJB2-related hearing loss.

Hematopoietic stem cell gene therapy for mucopolysaccharidosis type II

Yohta Shimada

Division of Gene Therapy, Research Center for Medical Sciences, The Jikei University School of Medicine
Associate professor

Mucopolysaccharidosis type II (MPS II), also known as Hunter syndrome, is an X-linked recessive lysosomal storage disease (LSD) caused by a deficiency of iduronate-2-sulfatase (IDS). MPS II is the most frequent mucopolysaccharidosis in East Asian countries including Japan. The progressive accumulation of glycosaminoglycans, which are substrates of IDS, induces various phenotypes involving hepatosplenomegaly, valvular heart disease, skeletal deformities, and central nervous system (CNS) involvement. Recently, novel enzyme replacement therapy (ERT) such as CNS-treatable enzyme for MPS II has been approved in Japan. However, there are still issues specific to ERT, such as the frequency of infusions and medical costs. To develop a one-time treatment that has a long-term effect on MPS II, we focused on hematopoietic stem cell gene therapy (HSC-GT), which is a promising treatment for the correction of systemic phenotypes in LSDs. We have previously demonstrated that HSC-GT can improve not only the biochemical changes but also their memory function in MPS II model mice. In addition, our study showed that HSC-GT improves bone abnormality in MPS II mice. Recently, we established the automated cell manufacturing process and performed a preclinical safety study for MPS II using gene-modified human CD34+ cells. We are preparing the clinical trial of HSC-GT for MPS II in Japan.

Atidarsagene Autotemcel (Hematopoietic Stem Cell Gene Therapy) Preserves Cognitive and Motor Development in Metachromatic Leukodystrophy with up to 12 Years Follow-up

Kent Christopherson, PhD

Executive Director, Global Medical Affairs, Orchard Therapeutics

Metachromatic leukodystrophy (MLD) is a rare neurometabolic disorder caused by a deficiency of arylsulfatase A (ARSA), leading to sulfatide accumulation and subsequently progressive demyelination, neurodegeneration, loss of motor and cognitive skills, and early death.

Long-term results (6.76 years, range 0.64-12.19) from an integrated analysis of 39 patients with early-onset MLD (19 late infantile, 20 early juvenile) treated with autologous hematopoietic stem cell gene therapy (atidarsagene autotemcel, “arsa-cel”) were compared with 49 untreated natural history (NHx) early-onset MLD patients.

Treated patients demonstrated stable engraftment of gene-corrected cells and sustained restoration of ARSA activity. Treatment of pre-symptomatic late-infantile (PSLI), pre-symptomatic early-juvenile (PSEJ), and early-symptomatic early-juvenile (ESEJ) MLD patients resulted in substantial improvements in motor and cognitive outcomes as compared to NHx patients. Most NHx patients experienced rapid motor and cognitive decline progressing to a severely debilitated state or death.

There were no serious adverse events related to arsa-cel, no malignancies, and no evidence of abnormal clonal expansion or replication-competent lentivirus. Most common adverse events (AEs) were consistent with the busulfan safety profile or symptoms of MLD. The only arsa-cel-related AEs were 6 events of transient and low titer anti-ARSA antibodies with no impact on pharmacodynamic or clinical outcomes. Three treated patients died, all considered unrelated to arsa-cel.

With up to 12 years follow-up in the earliest treated patient and cumulative 251 patient-years of follow-up, arsa-cel shows a favorable benefit-risk profile with clinically meaningful, sustained efficacy, preventing severe motor and cognitive impairment, preserving speech, and slowing disease progression in early-onset MLD patients.

Results from ongoing gene therapy clinical trials in patients with rare diseases: Mucopolysaccharidosis Type IIIa (MPS IIIa), Glycogen Storage Disease Type Ia (GSDIa), Ornithine Transcarbamylase (OTC) Deficiency, and Wilson Disease

Eric Crombez

Ultragenyx Pharmaceutical Inc. Novato, California United States

Introduction: AAV-based gene therapies are being investigated for various inborn errors of metabolism and neurologic disorders.
MPS IIIA is a lysosomal storage disease resulting in toxic accumulation of heparan sulfate (HS) in the brain, leading to irreversible neurocognitive decline and early death. UX111 is an investigational AAV9 vector expressing the lysosomal enzyme *N-sulfoglucosamine sulfohydrolase (SGSH)* transgene.
GSDIa results from a deficiency of glucose 6-phosphatase which is essential for glycogenolysis and gluconeogenesis, resulting in severe fasting intolerance. DTX401 is an investigational AAV8 vector expressing the *G6PC* transgene.
OTC deficiency is a urea cycle disorder resulting in episodic hyperammonemia that can be life threatening and cause cumulative and irreversible neurocognitive damage. DTX301 is an investigational AAV8 vector expressing the *OTC* transgene.
Wilson disease is a disorder of copper metabolism caused by mutations in the *ATP7B* gene that can lead to liver disease, neurological symptoms, and psychiatric disorders. UX701 is an investigational AAV9 vector expressing the *ATP7B* transgene.

Methods: Intravenous infusion of UX111 is being evaluated for safety/efficacy in a global phase 1/2/3 trial in children with MPS IIIa (NCT02716246).
A single DTX401 infusion in adults with GSDIa was evaluated for safety/efficacy in a global phase 1/2 gene therapy trial (NCT03517085) and a long-term follow-up (LTFU) study (NCT03970278).
DTX301 was evaluated for safety/efficacy in a global phase 1/2 trial in adults with late-onset OTC deficiency (NCT02991144), with an ongoing LTFU study (NCT03636438), and a phase 3 trial in children and adults currently enrolling (NCT05345171).
UX701 is being evaluated for safety/efficacy in a phase 1/2/3 trial in adults with Wilson disease (NCT04884815).

Results: UX111 for MPS IIIa: Cerebrospinal fluid (CSF) HS exposure was reduced by ≥50% versus baseline, and cognitive skills were stabilized or improved in 17 children in the modified ITT group relative to untreated children. The only treatment-related adverse event ≥ grade 3 was one event of increased alanine aminotransferase that resolved.
DTX401 for GSDIa: In 12 enrolled participants, mean (SD) total actual daily cornstarch intake reduction from baseline to last available timepoint, (~5 years for three participants) was 71.5% (23.7), $p<0.0001$. All participants experienced a treatment-emergent adverse event (TEAE) and a related TEAE; however, no infusion- or treatment-related serious adverse events were reported.
DTX301 for OTC deficiency: Seven of eleven participants had a meaningful and durable clinical response to DTX301 with up to ~7 years follow-up. Four were Complete Responders (discontinued ammonia-scavenging drugs and liberalized diet) and three were Responders (≥50% reduction in baseline disease management). No treatment-related serious AEs, dose-limiting toxicities, or infusion-related events were reported.
UX701 for Wilson disease: Six of 15 participants completely tapered off standard-of-care (SOC) treatment with chelators and/or zinc therapy. In participants who tapered off SOC, non-ceruloplasmin bound copper stabilized to normal, healthy levels. There were no unexpected treatment-related adverse events and no significant immunologic safety events.

Conclusions: Gene therapies have been shown to be safe and effective across multiple disease states and can target different organs, including the liver and brain, and may offer new hope for patients with no currently approved therapeutic options.

Complete normalisation of GM1 ganglioside storage through AAV expressing a blood-brain barrier-penetrating enzyme in mice

Saki Matsushima

Division of Gene Therapy, Research Center for Medical Sciences, The Jikei University School of Medicine, Assistant Professor

GM1 gangliosidosis is a lysosomal storage disorder (LSD) and caused by genetic defects in the lysosomal β-galactosidase (βgal) resulting in accumulation of mainly GM1 ganglioside (GM1) in neural cells. GM1 accumulation in the brain induces a rapid decline in psychomotor functions, seizures, and premature death. There is no therapy available.

Although enzyme replacement therapy (ERT) is approved for other LSDs, the effect on the CNS has been limited due to the blood-brain barrier (BBB). Here we assessed the therapeutic efficacy of systemic infusion of an AAV vector expressing BBB-penetrable enzyme under controlled by liver specific promotor to model mice. The BBB-penetrable enzyme consisted of the variable region of the anti-transferrin receptor-antibody fused with βgal. As a result, GM1 accumulation was completely normalized, and the neurological functions and their survival were improved. This therapeutic approach is expected to apply for the treatment of CNS involvement of other LSDs.

Part I: Potent Gene Therapy development for Menkes Disease: Preclinical Data and First-in-Human Study.
Part II: Accelerating Gene Therapy Development with VectorBuilder.

Miho Matakatsu, Ph.D.[1], Xiaozhu Chen, M.S.[2], Austin Gao, Ph.D.[2], Irene Gu[2], Jim Luo[2], Nanette Zheng, M.S.[2], Shiqi Li, MD.[3], Sanbin Wang, MD.[3], Bruce T. Lahn Ph.D.[4]

[1] VectorBuilder Inc., and Vector Builder Japan Inc.
[2] Lantu biopharma (Guangzhou) Co., Ltd.
[3] 920th Hospital of Joint Logistics Support Force of People's Liberation Army of China
[4] VectorBuilder Inc.

Part I: Menkes syndrome (MD) is a rare X-linked copper metabolism disorder caused by *ATP7A* gene mutations that result in nervous system defects. Early interventions with high dosage Copper-supplement extended survival, however the overall disease burden remains substantial. To date, no other effective treatment is available for MD. We designed and developed several AAV therapeutic candidates to overcome large ATP7A gene delivery. Preclinical studies showed efficient CNS-targeted transduction of AAV in a mouse model of MD. All mice treated with AAV together with a low dose of copper supplement increased survival significantly compared to the low dose of Cu-supplement alone and untreated group. After preclinical *in vitro* and *in vivo* studies, we evaluated the safety and efficacy of a single dose of LTGT06 in one 3-year-old male MD patient. The patient is still alive 2.5 years after treatment. Motor function improvement from baseline was observed post-treatment. With excellent safety profiles, strong efficacy in the mouse model, and signs of efficacy in a single human patient, AAV-based gene therapy shows strong promise for treating MD.

Part II: VectorBuilder is a full-service CDMO with extensive experience in cGMP vector manufacturing. Operating several state-of-the-art facilities, we have supported many customers along their entire drug-discovery pipelines, going from research-grade vectors for early discovery, to GMP-like vectors for preclinical testing, to full GMP-grade vectors for clinical trials. We have provided IND-enabling vectors to a worldwide client base in the US, Europe, Japan, China and South Korea. Our CDMO services include process development, analytical development, cell banking, fill/finish and regulatory support.

Roche's reflections on preparing for a future with gene therapy in Duchenne muscular dystrophy

Alex Murphy

Senior Clinical Director, Roche Pharmaceuticals UK.

Duchenne muscular dystrophy (DMD) is caused by mutations in the dystrophin-encoding DMD gene, a protein essential for muscle fibre function and protection. Delandistrogene moxeparvovec (developed by Sarepta Therapeutics and Roche), approved in the USA and other countries, is an rAAVrh74 vector-based gene therapy shown to stabilise or slow DMD progression.

The rAAVrh74 vector, distinguished by its low seroprevalence, provides broad muscle tissue distribution. The MHCK7 promoter drives transgene expression selectively in skeletal, respiratory and cardiac muscle. The delandistrogene moxeparvovec transgene encodes the delandistrogene moxeparvovec micro-dystrophin.

Across clinical trials to date (ambulatory patients aged ≥4–<8 years: Study 101 [Phase 1/2a, NCT03375164], Study 102 [Phase 2, NCT03769116], ENDEAVOR Cohort 1 [Phase 1b, NCT04626674], EMBARK [Phase 3, NCT05096221]), robust delandistrogene moxeparvovec transduction efficiency, transgenic micro-dystrophin protein expression and sarcolemmal localisation were observed up to Week 60. Pooled analysis (Study 101, 102, ENDEAVOR Cohort 1 [N=52]) vs. propensity-score-weighted external controls (N=105) suggested beneficial DMD trajectory modification. In EMBARK, although delandistrogene moxeparvovec (n=63) did not reach statistical significance versus placebo (n=62) in the primary endpoint (change from baseline to Week 52 in North Star Ambulatory Assessment total score), clinically meaningful benefit was evident on secondary functional endpoints. Across studies, adverse events (AEs) were medically manageable with appropriate monitoring and treatment. There were no clinically relevant complement activation AEs, deaths or study discontinuations.

Results suggest beneficial modification of DMD trajectory with a consistent safety profile. Ongoing studies, including ENVOL (Phase 2, NCT06128564) and ENVISION (Phase 3, NCT05881408), are assessing delandistrogene moxeparvovec across a wider population.

Clinical development of Onasemnogene abeparvovec and Voretigen neparvovec

Ken Tsuchida

Japan Program Clinical Head, Neuroscience & GTx clinical development, Novartis Pharma K.K.

Saori Ito

Sr. Japan Program Clinical Head, Neuroscience & GTx clinical development, Novartis Pharma K.K.

Onasemnogene Abeparvovec IV (OA-IV) was approved in 2020 as the first gene therapy product for the treatment of spinal muscular atrophy (SMA) in Japan. In addition, OA-IV is the first approved product for pre-symptomatic SMA in Japan.
SMA is caused by mutations in the *survival motor neuron gene 1 (SMN1)*, and SMA patients cannot produce the functional SMN protein sufficiently and are characterized by muscle weakness and Muscle atrophy.
OA-IV, an adeno-associated virus vector serotype 9 (AAV9) product, delivers the functional copy of *SMN* gene to motor neuron, by one time administration.
In this time, the summary of clinical study data of OA-IV will be presented. In addition, preliminary data of post marketing survey(PMS) and the current medical environment of SMA will be share.
Voretigene neparvovec (VN) is the first approved ocular gene augmentation therapy for patients with *RPE65* mutation-associated inherited retinal dystrophy (IRD), IRDs are rare heterogeneous disorders characterized by progressive retinal degeneration, and mutations that can lead to IRDs have been identified in >260 genes. Clinical manifestations of *RPE65* mutation-associated IRDs include night blindness or a concentrically constricted visual field (VF).
VN is a recombinant adeno-associated virus vector serotype 2 (AAV2) containing human RPE65 cDNA and induces the production of a functional RPE65 enzyme, thus allowing the restoration of the visual cycle.
Here, the overview of Japan clinical development and clinical study data of VN will be presented.

Guiding the Path of Gene Therapy -Supporting Patients and Families-

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Advancements in genomic medicine have led to genomic information playing a role not only in diagnosis but also in the assessment of disease severity, prevention, and selection of treatment options. In this expanding clinical application of genomic information, gene therapy has emerged as a novel option for treating hereditary diseases. As gene therapy becomes integrated into clinical practice, the importance of genetic counseling is growing to help patients and their families understand and accept complex treatment processes while coming to terms with their conditions.

In gene therapy for hereditary diseases, identifying pathogenic variants is essential for some conditions, and early diagnosis through genetic testing serves as the foundation for treatment in such cases. However, genetic testing can impact not only the individual patient but also their relatives, necessitating careful consideration of these aspects when conducting such tests. Therefore, pre-test genetic counseling plays a crucial role in explaining the purpose of testing, selecting the appropriate timing, and ensuring thoughtful disclosure of results. This approach fosters trust, supports patients and families in accepting their conditions, and facilitates their journey toward gene therapy.

Moreover, genetic counseling must accurately convey the benefits, risks, and limitations of gene therapy, while addressing psychosocial and ethical challenges as central themes of the counseling process. Gene therapy is not a standalone intervention performed by a single department or discipline but is instead carried out within the framework of multidisciplinary team-based care. Genetic counseling should also be integrated into this team-based approach to provide patients and their families with comprehensive and continuous support.

Precision Genetic Engineering of Hematopoiesis to Treat Human Disease

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Genetic engineering of hematopoietic stem cells (HSC) with lentiviral vectors has been providing substantial benefit to growing numbers of patients affected by primary immunodeficiencies, hemoglobinopathies and storage disorders. Long-term follow up shows stable hematopoietic reconstitution by high numbers of corrected HSC without signs of clonal expansion or exhaustion. Precise engineering by gene editing may further improve the reach and safety of HSC gene therapy by achieving in situ gene correction or targeted transgene integration. Homology-driven editing, however, remains limiting in long-term HSC and the genetic outcome at target sites heterogenous and, for some by-products, potentially genotoxic. Template delivery by Integrase-defective lentiviral vectors rather than AAV6 and the use of lipid nanoparticles instead of electroporation may increase safety and efficiency of the procedure. Coupling selection for the intended edit and purging adverse outcomes may provide a preferred path towards clinical application of this currently unique modality enabling long-range edits. On the other hand, the emergence of base and prime editors that bypass the requirement for DNA double-strand breaks (DSB) allows editing single/few mutant nucleotides with limited activation of DNA damage response. We have shown, however, that DSBs are significantly lowered but not abrogated. Moreover, the expression of constitutive deaminase domains within the editors may impact the mutagenic load of treated cells. While these potentially genotoxic outcomes can be mitigated by optimizing expression and culture conditions, they should be better investigated and monitored in emerging clinical applications.

Another long-sought goal of HSC gene therapy is to make space for the infused cells without relying on genotoxic conditioning, which entails acute and chronic serious adverse effects. We have shown that HSC mobilization opens a window of opportunity for engraftment of donor cells, which can effectively outcompete those in the circulation for engraftment in the depleted niches. Competitive advantage results from the rescue in culture of a detrimental impact of mobilizing agents on HSC and can be further enhanced by transient over-expression of engraftment effectors. These findings were obtained in human hematochimeric mice and are currently being investigated in non-human primates.

Overall, our work should advance HSC gene therapy by a combination of transformative approaches leveraging on precision genetic engineering while alleviating the morbidity of the procedure, broadening application to several diseases and patients worldwide